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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/615,718
Filing Date: July 09, 2003
Appellant(s): WALDMANN ET AL.

Raymond J. Lillie
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 09 August 2010 appealing from the Office action mailed 06 March 2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 2-5 and 11 are cancelled.

Claims 1, 6-10, 12-15 and 17 are rejected.

Claim 16 remains withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN

REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

Hale G. "Synthetic Peptide Mimotope of the CAMPATH-1 (CD52) Antigen, A Small Glycosylphosphatidylinositol-anchored Glycoprotein" Immunotechnology, Vol. 1 (1995), pp. 175-187

Li et al. "B-Endorphin Omission Analogs: Dissociation of Immunoreactivity From Other Biological Activities" Proc. natl. Acad. Sci. USA, Vol. 77, No. 6 (June 1980), pp. 3211-3214.

Lederman et al. "A Single Amino Acid Substitution in a Common African Allele of the CD4 Molecule Ablates Binding of the Monoclonal Antibody OKT4" Molecular Immunology, Vol. 28, No. 11 (1991), pp. 1171-1181.

(9a) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 6, 9-10 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Hale G (Immunotechnology, 1:175-187, 1995).

Hale G teaches an anti-CD52 humanized antibody, CAMPATH-1H, reversibly bound by the synthetic peptide, QTSSPSAD, a CD52 mimotope that inhibits binding of CAMPATH-1H to human lymphocytes expressing CD52 by about four fold and the antibody is disclosed in various buffers including PBS, which are reasonably interpreted to be a "pharmaceutically acceptable carrier" (see entire document, particularly pg. 176, col. 2, 2nd paragraph, pg. 179, col. 2), pg. 183,

col. 2, 2nd paragraph and Fig. 8). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Thus, the CAMPATH-1-CD52 mimotope bound complex taught by Hale necessarily reduces side effects and produces a therapeutic effect by binding to CD52 and the amount of antibody that binds to the target increases as the mimotope is displaced from the antigen-binding site of the antibody, all intrinsic properties of the CAMPATH-1-CD52 mimotope bound complex of Hale. Further, the intended use of the therapeutic antibody as a "pharmaceutical" as recited in the preamble is given no patentable weight (see MPEP 2111.02). A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951)

Thus, Hale anticipates the claims.

(10a) Response to Argument

Appellant states that the present invention is directed to a pharmaceutical composition comprising a therapeutic antibody that binds to a therapeutic target, wherein the therapeutic antibody is modified with a peptide that inhibits binding of the antibody to the therapeutic target and is effective for reducing an immune response against the antibody and for producing a therapeutic effect by binding to the therapeutic target. Although Hale discloses the binding of CAMPATH antibodies to mimotopes of the CD52 antigen, the purpose of the binding studies disclosed in Hale were to characterize the CD52 epitope bound by CAMPATH more precisely, and to construct analogues of such epitope that would be useful in assays and for purifying CAMPATH antibodies, as well as studies for the antigen-binding site. Further, Appellant states that Hale is directed solely to studying the binding of CAMPATH antibodies to CD52 mimotopes in order to aid in the development of assays, of methods of purifying CAMPATH antibodies, and in studying the antibody-antigen interaction between CAMPATH antibodies and

the CD52 antigen or mimotopes thereof. Appellants' arguments have been fully considered but are not found persuasive. The fact that Hale was concerned with a different purpose or doesn't recognize that the CAMPATH humanized antibody bound to the synthetic peptide, QTSSPSAD, is effective for reducing an immune response against the antibody and for producing a therapeutic effect by binding to the therapeutic target, does not distinguish the claimed pharmaceutical comprising a therapeutic antibody bound to a peptide that inhibits binding of the antibody to a therapeutic target, from the anti-CD52 humanized antibody, CAMPATH, reversibly bound by the synthetic peptide, QTSSPSAD, a CD52 mimotope that inhibits binding of CAMPATH to human lymphocytes expressing CD52 (i.e., "therapeutic target") by about four fold, wherein the antibody is taught in various buffers including buffered saline (PBS) (i.e., reasonably interpreted to be a "pharmaceutically acceptable carrier") by Hale. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art... However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. V. IRECO*, Inc 51 USPQ2d 1943 (Fed. Cir. 1999).

Again, the claims do not distincguish the antibody over the antibody of Hale. The claims merely require the therapeutic antibody be modified with a peptide bound to the antibody combining site and which reduces binding of the antibody to the therapeutic target. Thus, the CAMPATH humanized antibody bound to the synthetic peptide, QTSSPSAD, a CD52 mimotope that inhibits binding of CAMPATH to human lymphocytes expressing CD52 (i.e., "therapeutic target") by about four fold (i.e., "reduces binding of the antibody to the therapeutic target") is a therapeutic antibody modified with a peptide bound to the antibody combining site and which reduces binding of the antibody to the therapeutic target, identical to the instantly claimed therapeutic antibody. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Thus, the CAMPATH -CD52 mimotope bound complex taught by Hale necessarily reduces side effects and produces a therapeutic effect by binding to CD52 and the

amount of antibody that binds to the target increases as the mimotope is displaced from the antigen-binding site of the antibody, all intrinsic properties of the CAMPATH-1-CD52 mimotope bound complex of Hale.

For these reasons and those already of record, the rejection is maintained.

(9b) Grounds of Rejection

Claims 1, 6-10, 12-15 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (see MPEP 2163).

In the instant case, the claims are drawn to a broad genus of pharmaceutical compositions comprising a therapeutic antibody being modified with a peptide that is effective for reducing side effects caused by the antibody and wherein the therapeutic antibody produces a therapeutic effect by binding to the therapeutic target. However, the written description in this case only sets forth one therapeutic antibody, humanized anti-CD52 antibody (CAMPATH-1H), which is modified by linking the antibody to the CD52 mimotope QTSSPSAD or the CD52 mimotope mutant QTSAAAVD and which reduces cytokine release (i.e., reduced side effect).

The specification on page 9 discloses that a compound may be a peptide or other molecule that is capable of binding to the antigen-binding site of the antibody and functions to inhibit binding of the antibody to the antigen. The specification on page 3 discloses that the term

"therapeutic" encompasses both treating an existing disease condition or disorder and preventing and/or reducing the severity of a disease condition or disorder. The specification on page 11 discloses that the term "antibody" includes all form of antibodies such as recombinant, humanized, chimeric antibodies and antigen-binding fragments thereof that are capable of binding a therapeutic target. Thus, the claims encompass an extremely large genus of therapeutic antibodies linked to a genus of peptides, and which is used for treating, preventing and/or reducing any disease condition or disorder. However, the written description of the present application only reasonably conveys a therapeutic humanized anti-CD52 antibody, CAMPATH-1H, modified by linking two different peptides, CD52 mimotope (QTSSPSAD) or CD52 mimotope mutant 9 (QTSAAAVD) in which the antibody-mimotope conjugate reduced the immune response (i.e., cytokine release) and had a therapeutic effect by binding CD52.

Thus, the instant disclosure does not provide sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus of therapeutic antibodies linked to just any "peptide" that inhibits the binding of the therapeutic antibody and has "reduced side effects" and "produces a therapeutic effect". See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. The description of humanized anti-CD52 antibody, CAMPATH-1H, modified by linking two different peptides, CD52 mimotope (QTSSPSAD) or CD52 mimotope mutant 9 (QTSAAAVD) and having the claimed properties is not representative of the entire genus because the genus is highly variable, inclusive to a variety of structurally and functionally divergent antibodies and immunoglobulin-based fusion proteins that are linked to just any peptide. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Clearly, one of skill in the art would not recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the single disclosed CAMPATH-1H-mimotope species.

Further, it is not sufficient to define a substance solely by its principal biological property, because an alleged conception having no more specificity than that is simply a wish to

know the identity of any material with that biological property. Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CAFC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function". Similarly, the function of inhibiting binding of a therapeutic antibody to the therapeutic target does not distinguish any peptide from others having the same activity or function and as such, fails to satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Structural features that could distinguish the therapeutic antibody-peptide complexes and conjugates in the genus from others in the protein class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure does not describe the common attributes or structural characteristics that identify members of the genus, and because the genus is highly variant, the function of the binding of "therapeutic antibody" and the function of the peptide alone are insufficient to describe the genus of therapeutic antibodies and peptides bound or linked thereto that "reduce side effects" and "produce a therapeutic effect". One of skill in the art would reasonably conclude that the disclosure of a single humanized anti-CD52 antibody-mimotope conjugate, does not provide a representative number of species of therapeutic antibodies linked or bound to a peptide to describe the claimed genus that reduces side effects and produces a therapeutic effect.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the humanized anti-CD52 antibody, CAMPATH-1H, linked to the CD52 mimotopes, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

(10b) Response to Argument

Appellant states that those skilled in the art understand readily that different antibodies will have different antibody combining sites, and that the location of the antibody combining site of an antibody can be determined by routine experimentation. Once the antibody combining site has been determined, one can modify the antibody by binding a peptide to the antibody combining site of the antibody by means known to those skilled in the art. In other words, once one skilled in the art has read what the modified antibody includes, one skilled in the art would be able to make the modified antibody by standard techniques known to those skilled in the art. Once the modified antibody is constructed, one skilled in the art would be able to determine through routine experimentation whether the peptide reduced binding of the antibody to the therapeutic target and reduced side effects caused by the antibody. Appellant concludes that the specification provides a written description of the invention. Appellants' arguments have been fully considered but are not found persuasive. Appellants' argument that one skilled in the art could determine the antibody combining site for different antibodies, modify the antibody by binding a peptide to the antibody combining site and determine whether the peptide reduced binding of the antibody to the therapeutic target and reduced side effects caused by the antibody seems to go more toward enablement than written description. That is, the argument seems intended to show that, following the teachings in the specification, those skilled in the art could have produced other therapeutic antibody-peptide pairs, and determined which (if any) would have the claimed properties, without undue experimentation. The instant rejection is based on lack of adequate written description, not lack of enablement. The written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v.*

Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991). *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.* (Fed. Cir. 2010) (en banc). The issue remains the lack of adequate written description in the instant application, not whether other antibodies have been or could be made according to the disclosure. "It is not a question whether one skilled in the art might be able to construct the patentee's device from the teachings of the disclosure of the application. Rather, it is a question whether the application necessarily discloses that particular device." *Id.* at 536. *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004).

The following is reiterated for convenience. The claims are drawn to a pharmaceutical comprising a therapeutic antibody being modified with a peptide that reduces binding of the antibody to the therapeutic target and is effective for reducing an immune response against the antibody and for producing a therapeutic effect by binding to the therapeutic target. Thus, the claims encompass an extremely large genus of therapeutic antibodies linked to a genus of peptides, disclosed for treating, preventing and/or reducing any disease condition or disorder. However, written description of the present application only reasonably conveys a single therapeutic humanized anti-CD52 antibody, CAMPATH-1H, modified by linking two different peptides, CD52 mimotope (QTSSPSAD) or CD52 mimotope mutant 9 (QTSAAAVD) in which the antibody-mimotope conjugate reduced the immune response (i.e., cytokine release) and had a therapeutic effect by binding CD52. Appellants' reliance on the description of a single species of humanized anti-CD52 antibody, CAMPATH-1H, modified by linking a CD52 mimotope (QTSSPSAD or QTSAAAVD) and having the properties and characteristics unique to the CAMPATH-1H-CD52 mimotope (QTSSPSAD or QTSAAAVD) interaction is not representative of the entire genus because the genus is highly variable, inclusive to a variety of therapeutic antibodies, having different therapeutic targets, functions and effects (i.e., agonistic, antagonistic, blocking, recruitment of effector cells, ect) and which are linked to any peptide, inclusive to peptides of varying lengths and chemical composition. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the

patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). The specification provides no other structural description of a therapeutic antibody being modified with a peptide that reduces binding of the therapeutic antibody to a therapeutic target, wherein the therapeutic antibody-peptide pair is effective for reducing side effects caused by the antibody and produces a therapeutic effect by binding to the therapeutic target, other than the ones specifically disclosed; in essence the specification simply directs those skilled in the art to go figure out for themselves what the claimed genus of therapeutic antibody-peptide pairs look like and which one's have the required functional characteristics. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 (written description requirement not satisfied by merely providing "a result that one might achieve if one made that invention"); *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming a rejection for lack of written description because the specification does "little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate").

Clearly, one of skill in the art would not recognize that Appellant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the single disclosed CAMPATH-1H-mimotope species. Therefore, only the humanized anti-CD52 antibody, CAMPATH-1H, linked to the CD52 mimotope QTSSPSAD or QTSAAAVD, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph.

(9c) Grounds of Rejection

Claims 1, 6-10, 12-15 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising

CAMPATH-1H (humanized anti-CD52 antibody), modified by linkage to a CD52 mimotope selected from QTSSPSAD and QTSAAAVD, does not reasonably provide enablement for all other therapeutic proteins and therapeutic antibodies modified (i.e., bound or linked) with just any peptide, wherein the therapeutic antibody has reduced side effects and produces a therapeutic effect by binding to the therapeutic target. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The instant claims are broadly drawn to a pharmaceutical composition comprising a therapeutic antibody being modified with a peptide that inhibits binding of the antibody to the therapeutic target, wherein the modified therapeutic antibody is effective for reducing side effects caused by the antibody and produces a therapeutic effect by binding to the therapeutic target. Thus, the scope of the claims encompasses pharmaceutical compositions comprising just any therapeutic antibody that is bound or linked to just any peptide that inhibits binding of the antibody to the therapeutic target and the modified antibody reduces side effects caused by the antibody and produces a therapeutic effect by binding to the therapeutic target. The teachings and exemplary guidance in the specification are limited to a humanized anti-CD52 antibody (CAMPATH-1H) linked to a CD52 mimotope, which reduces binding to CD52, but is competitively displaced by CD52 *in vivo* due to more favorable association and dissociation binding kinetics and the CAMPATH-1H-mimotope conjugate reduces cytokine release (e.g., reduced side effects). There is no guidance or direction of any other therapeutic antibody bound

or linked to just any peptide that inhibits binding of the antibody to the therapeutic target that reduces side effects and produces a therapeutic effect by binding to the therapeutic target. Thus, the scope of the claims is extremely broad relative to the teachings and guidance provided in the disclosure. The scope of the claims must bear a reasonable correlation with the scope of enablement. See *In re Fisher*, 166 USPQ 19 24 (CCPA 1970).

The state of the prior art is such that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Lederman et al (Molecular Immunology 28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980) disclose the dissociation of immunoreactivity from other activities when constructing analogs (see entire document). Thus, the state of the art recognized that it would be highly unpredictable that linkage of just any peptide to a therapeutic antibody specific for a therapeutic target or even the linkage of a particular peptide with just any therapeutic antibody would provide the requisite antibody-antigen association having the appropriate affinity wherein upon administration of such modified therapeutic antibody, the peptide would inhibit by obstructing the binding site of the therapeutic antibody, thereby "reducing side effects" and displacement of the peptide from the binding site upon binding to the therapeutic target produces a therapeutic effect. One of skill in the art could not predictably extrapolate the teachings in the specification limited to a humanized anti-CD52 antibody linked to a CD52 mimotope to then broad class of therapeutic antibodies bound or linked to a peptide that inhibits binding of the antibody to its therapeutic target and wherein the antibody gradually accumulates on cell-bound or target antigen due to favorable association and dissociation constants relative to that of the peptide thereby "reducing side effects" and producing a therapeutic effect. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Lederman et al and Li et al, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed pharmaceutical compositions comprising a therapeutic antibody bound or linked to a peptide that inhibits binding of the antibody and produces a therapeutic effect by binding to the therapeutic target with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed compositions and absent working examples providing evidence which is reasonably predictive of the claimed compositions, commensurate in scope with the claimed invention.

(10c) Response to Argument

Appellant asserts that one skilled in the art would know how to modify antibodies other than CAMPATH-1H in accordance with the present invention. Appellant states that one skilled in the art could determine by routine experimentation how to bind peptides to antibody combining sites of other antibodies to provide modified antibodies and then one could test the modified antibody to determine whether binding the therapeutic target has been reduced. Appellant also states that the fact that not every modified antibody is within the scope of the claimed invention does not mean that the present invention is not enabled. Appellant asserts that the examiner has confused the fact that not all modified antibodies are within the scope of the present invention with the legal standard for enablement. Appellant also points out that the examiners statement that even minor changes in an epitope sequence may affect antigen binding function has no relevance with respect to enablement. Appellants' arguments have been fully considered but are not found persuasive. As an initial matter, the examiner acknowledges that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). Although, typically, inoperative embodiments are excluded by language in a claim (e.g., preamble), the

scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. However, claims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

In the instant case, the claims encompass a large genus of therapeutic antibodies and peptide pairs, wherein just any peptide reduces binding of just any therapeutic antibody to a therapeutic target, reduces side effects caused by the therapeutic antibody and produces a therapeutic effect by binding to the therapeutic target, encompassing significant numbers of inoperative species as evidenced by the art. For example, Lederman et al (Molecular Immunology 28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980) disclose the dissociation of immunoreactivity from other activities when constructing analogs (see entire document). Therefore, even one amino acid difference in the peptide used for the modification of the therapeutic antibody could dramatically change the affinity or binding to the antibody combining site. Appellants' argument that the above examiner's statement pertaining to the fact that one amino acid difference in the peptide used for the modification of the therapeutic antibody could dramatically change the affinity or binding to the antibody combining site has no relevance with respect to enablement is curious given that one of the Wands factors for determining whether a disclosure meets the enablement requirement is the predictability or unpredictability of the art. Thus, given that the claims are directed to a large genus of undefined peptides and undefined therapeutic antibodies, wherein the claimed invention depends on antibody-antigen (e.g., peptide) interactions and a particular affinity, the teachings of Lederman and Li are relevant to the presently claimed subject matter and the unpredictability within the large genus of modifying any antibody with just any peptide, such that the peptide modifies the therapeutic antibody to reduce binding to the therapeutic target, reduces some unknown side effects caused by the therapeutic antibody and produces a some therapeutic effect by binding to the therapeutic target. Again, Appellants' 'proof of

concept', which is specific to the unique binding properties of the CAMPATH-1H antibody and CD52 function, could not be predictably extrapolated by those skilled in the art to the genus of peptides for modifying the genus of therapeutic antibodies or even for a particular therapeutic antibody. Applicant has not provided any guidance or direction as to how the properties of the CAMPATH-1H-CD52 mimotope interaction are predictive of the interaction between a particular therapeutic antibody and a given peptide sequence, such that the peptide modifies the therapeutic antibody to reduce binding to the therapeutic target, reduces side effects caused by the therapeutic antibody and produces a therapeutic effect by binding to the therapeutic target. There is insufficient evidence or nexus between the properties of the CAMPATH-1H-CD52 mimotope interaction and making and using any other therapeutic antibodies bound to just any peptide that inhibits binding of the therapeutic antibody to the therapeutic target, reduces side effects caused by the therapeutic antibody, and produces a therapeutic effect by binding to the therapeutic target. The specification does not enable the genus because where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one particular species, what other species will work. See MPEP 2164.03.

"[T]o be enabling, the specification.., must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *Wright,* 999 F.2d at 1561, 27 USPQ2d at 1513 (emphasis added), *quoted in Genentech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed." *In re Vaeck,* 947 F.2d 488,496 & n. 23, 20 USPQ2d 1438, 1445 & n. 23 (Fed. Cir. 1991), *quoted in Enzo Biochem Inc. v. Calgene, Inc.,* 188 F.3d 1362, 1372, 52 USPQ2d 1129, 1138 (Fed. Cir. 1999).

In view of the broad scope of the claims at issue, the lack of the predictability of the art to which the invention pertains as evidenced by Lederman et al and Li et al, the lack of guidance and direction provided by Appellant, and the absence of working examples, undue experimentation would be required to practice the claimed pharmaceutical comprising a therapeutic antibody bound or linked to a peptide that inhibits binding of the therapeutic antibody to the therapeutic target, reduces side effects caused by the therapeutic antibody, and produces a therapeutic effect by binding to the therapeutic target with a reasonable expectation of success, absent a specific and detailed description in Appellant's specification of how to effectively practice the claimed pharmaceutical and absent working examples providing evidence which is reasonably predictive that the claimed pharmaceutical comprising a therapeutic antibody bound or linked to a peptide inhibits binding of the therapeutic antibody to the therapeutic target, reduces side effects caused by the therapeutic antibody, and produces a therapeutic effect by binding to the therapeutic target, commensurate in scope with the claimed invention.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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